REMARKS

Following entry of the amendment requested herein, Claims 1–16, 18 and 20–31 are pending in the present application. Of the pending claims, Claims 1-16 and 26-31 are withdrawn herein.

Claim 20 is amended to be a dependent claim depending from Claim 18.

Claims 18 and 21-25 are amended to enhance clarity of the claim language.

No new matter is added, and no change in inventorship is believed to occur, as a result of any amendment herein.

RESPONSE TO OFFICE ACTION DATED 24 DECEMBER 2009

1. Response to Election/Restriction Requirement

The Office is requiring Applicant to restrict these claims, under 35 U.S.C. §121, to one of the following groups of inventions:

I. Claims 1-16 and 26-31, drawn to a transdermal therapeutic system, classified in class 424, subclass 449.

II. Claims 18 and 24, drawn to a method for preparing a TTS, classified in class 424, subclass 449.

III. Claims 20-23 and 25, drawn to a method for preparing a TTS, classified in class 424, subclass 449.

Applicant respectfully traverses the grouping laid out in the present Office Action, particularly grouping as to Groups II and III. It is respectively submitted that Groups II and III, at least, should be one group for substantive examination purposes because both groups are sufficiently closely related to not place an undue search or examination burden on the Office. More specifically, they not only share common features as a method to produce a TTS but also fall under the same U.S. search classification (class 424, subclass 449), as indicated by the Examiner. Furthermore, Claim 20 (*i.e.*, the independent claim of Group III) is amended herein to depend from Claim 18 (*i.e.*, the independent claim of Group II), and Groups II and III now have only one independent claim. In view of the claim structure having one independent claim, there would be no undue search burden on the Office to examine the proposed groups.

Provided that the Office combines Groups II and III as a single group, Applicant elects, without traverse, to prosecute the Group II and III invention (*i.e.*, Claims 18 and 20-25) drawn to a method for preparing a TTS. Applicant reserves the right to pursue one or more continuing applications directed toward any unelected subject matter.

Applicant is further required to elect a single species. By election of a species herein, no admission is made or should be inferred that Applicant considers the invention to be limited to that species. Applicant provisionally elects a process for preparation described in Example 4. Claims 18 and 20-25 are readable on the provisionally elected process of Example 4.

Example 4 describes a species process falling under the generic scope of Claim 18, where the elected process comprises species components as opposed to generic components. Illustratively, the summary below on Example 4 shows embracement of the claims (claimed features are underlined):

- "Producing SXS- or EVA-Based Hot-Melt TTS in Lab Quantities **[0194]** 8.5 g of the SXS hot-melt adhesive (Duro-Tak 34-4230 by National Starch & Chemical) or 8.5 g of the EVA hot-melt adhesive was heated (Claims 18 and 20) at 160°C. (Claims 21 and 24) for about 20 minutes until a homogeneous melt was obtained. (Claims 18 and 20) 1.5 g or, respectively, 1.65 g of Rotigotine base was added (Claims 20 and 22) and the mixture was manually homogenized. The mixture was then laminated onto a preheated chill roll (120°C.). 5 cm^2 patches (for permeation experiments) and 20 cm^2 patches (for determining the patch weight) were then cut out. The matrix weight is shown in Table 2 below." (paragraph [0194], emphasis added)

TABLE 2

Lot No.	Adhesive	Internal-Phase Content [% w/w]	Theoretical Active-Substance Content [% w/w]	Actual Active-Substance Content [% w/w]	Weight (n = 10) [g/m^2]	Purity % (220 nm/272 nm)
20103041	SXS	—	15	14.96	85	94.9/94.3
20103048	EVA	—	16.2	18.24	58	98.1/99.7
20103047	EVA	—	16.2	15.96	127	98.8/99.9

(Claims 23 and 25, see purity % column)

For the reasons set forth above, reconsideration of the pending application is respectfully requested.

2. Obviousness-type double patenting

Claims 1–16, 18 and 20–25 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 28–59 of copending application Serial No. 10/523,908. Claims 1-16 are withdrawn and the rejection against the remaining claims (Claims 18 and 20-25) is respectfully traversed.

The rejection is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the co-pending application issues as a patent. Furthermore, the pending claims under consideration, *i.e.*, Claims 18 and 20-25, are all directed to a method of preparing a TTS, whereas the pending claims under consideration of copending application Serial No. 10/523,908, *i.e.*, Claims 28-36 and 41, are all drawn to a TTS (*i.e.*, an article invention). Therefore, the provisional obviousness-type double patenting rejection is no longer applicable to this application in view of the bifurcated subject matter claimed in each application. Reconsideration of this rejection is respectfully requested.

3. Rejection under 35 U.S.C. §103(a) over Chen in view of Schollmayer and Noel

Claims 1–16, 18 and 20–31 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,807,570 ("Chen"), in view of U.S. 2004/0048779 ("Schollmayer") and U.S. Patent No. Re. 36,754 ("Noel"). Claims 1-3 and 6-16 are withdrawn herein and the rejection against the remaining claims (*i.e.*, Claims 18 and 20-25) is respectfully traversed.

3.1. Not all claimed features are taught or suggested by the cited documents

Claim 18 is not obvious over the alleged combination of Chen, Schollmayer and Noel (even if motivation existed for such combination, which is not admitted herein), at least because the cited documents fail to teach or suggest all of the claimed features. To establish a

prima facie case of obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); *In re Wilson*, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970) ("All words in a claim must be considered in judging the patentability of that claim against the prior art").

The alleged combination fails to teach or suggest all claimed features of Claim 18. In particular, the method of preparing a rotigotine-containing TTS of Claim 18 expressly requires melting and homogenizing the components of the cement matrix and rotigotine without solvent at a temperature between 70°C and 200°C.

Chen does not teach a rotigotine hot-melt process, and the active ingredient included therein is not rotigotine either.

Schollmayer does not teach a rotigotine hot-melt process.

Lastly, Noel mentions hot-melt silicone pressure sensitive adhesive compositions, but fails to teach a method of preparing a rotigotine-containing TTS by a hot-melt process. Thus, the alleged combination fails to teach all claimed features, particularly a solvent-free hot melt process for a rotigotine-containing TTS, and Claim 18 is not *prima facie* obvious over the alleged combination.

3.2. Chen cannot be a primary 35 U.S.C. §103(a) reference

Claim 18 is drawn to a method of preparing a rotigotine-containing TTS and a key feature of the claimed method is melting and homogenizing the components of the cement matrix and rotigotine without solvent at a temperature between 70°C and 200°C. However, Chen does not teach even a single element of the key feature which includes, for example, "melting," "homogenizing," "components of the cement matrix," "rotigotine," "without solvent" and "a temperature between 70°C and 200°C." In other words, Chen's methods are essentially different from the claimed method which makes Chen not modifiable. Therefore, none of Chen's teachings can be used to reject the claimed method.

The present rejection further cites Schollmayer and Noel as secondary §103 references, but these documents would not be useful unless there is anything citable from the main publication, *i.e.*, Chen. In this regard, Applicant respectfully requests that the Office

remove Chen from the primary §103(a) reference status and withdraw all rejections based on Chen.

3.3. Disclosures are not combinable because teachings are incompatible

Even if Chen teaches anything citable against the claimed invention, which Applicant does not admit, Schollmayer and Noel are not properly combinable with Chen because Chen, Schollmayer and Noel teach substantially incompatible methods for preparing a transdermal system.

For example, Chen is incompatible with Noel. The Examiner admits that Chen is silent with respect to the teaching of a hot-melt process (Office Action, p. 11). Chen teaches a drug dispersed in an adhesive matrix by a non-hot-melt process, whereas Noel describes a matrix-dispersion (col. 6, lines 8-15) and a reservoir system (col. 6, lines 16-64). Noel mentions adhesive matrix formed by a hot-melt process but the matrix is for different transdermal systems. More importantly, Noel fails to teach, not to mention rotigotine, any specific drug to be included in the matrix. It should be understood that the application of hot-melt processes for rotigotine is not obvious because of rotigotine's physical/chemical properties (this point is further discussed in Sec. 3.5 below). No reason or teaching is provided to reconcile these disparate approaches.

As shown above, the methods of Chen, Schollmayer and Noel are substantially different and even incompatible. Therefore, it should not be allowed to take pieces from those publications and construct a method with the pieces in a hindsight manner unless the Office provides reason(s) why such piecemeal items can be combined despite the incompatibility.

3.4. No rationale to modify the cited art to include the missing subject matter

Where the combined references are missing claimed features, a case of obviousness requires an apparent reason, based either on the references themselves or on the general knowledge in the art, by which an ordinary skilled artisan would modify the references to include the missing subject matter. See *KSR Int'l Co. v. Teleflex Inc.,* 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (obviousness includes determining whether there was an apparent reason to combine known elements in the fashion claimed).

The primary document relied upon, Chen, relates to a ropinirole-containing transdermal system, and methods described therein do not involve a hot-melt process. Chen does not provide any guidance to a person having ordinary skill to solve problems associated with a hot-melt process for oxidation-sensitive drugs. Given that such missing features are very important for the claimed invention, Chen cannot be the primary document in this §103(a) rejection. In other words, Chen is not modifiable to become a hot-melt process for preparing a rotigotine-containing TTS without solvent.

Furthermore, the alleged combination, even if properly combinable, is devoid of any suggestion or appreciation of (1) melting rotigotine and cement matrix and (2) using a solvent-free process. The present Action fails to provide any basis for an ordinary skilled artisan to forgo such use of solvent or include the present melting processes, as required by *In re Kahn*, 441 F3d 977, 78 USPQ2d 1329 (Fed. Cir. 2006) ("rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning to support the legal conclusion of obviousness"). In contradistinction, the present specification illustrates several advantages and benefits over solvent-based systems (see specification, paragraph **[0008]**). Absent the articulated reasoning required by *In re Kahn* and by *KSR*, the combination of Chen, Schollmayer and Noel cannot support a presumption of *prima facie* obviousness.

3.5. Predictability of outcome required for *prima facie* obviousness is lacking

Rotigotine is known to be very susceptible to oxidation; that is, rotigotine tends to decompose at a higher temperature in oxidative fashion. Thus, it could not have been predicted that rotigotine would lend itself to processing by the present hot-melt methods at a temperature up to 160°C. Further, it could not have been predicted that rotigotine would be released from matrices prepared in this way in a continuous fashion and at a therapeutically desirable rate (specification, paragraph **[0026]**). However, it was surprisingly discovered by the present inventors that rotigotine is compatible with hot-melt technique. Rotigotine remains stable on melting and is present in the resulting matrix at a purity level that is routinely better than 98% and generally over 99%, as measured at 220 nm and 272 nm by HPLC (specification, paragraph **[0027]** and Tables 2, 3 and 4). It should be understood that

high drug-loaded solid dispersion with high drug dissolution enhancement is not an easy task since the drug presented in such a system. Despite these difficulties, Applicant has provided a method for preparing a TTS that comprises a rotigotine-containing cement matrix with a high concentration of rotigotine and with high drug dissolution enhancement. Also, the claimed method enables a cement matrix to include higher rotigotine concentrations than other layers prepared by solvent-based processes. Furthermore, the present invention provides improved safety and processing times (specification, paragraph **[0030]**).

None of these advantageous outcomes were predictable from each of Chen, Schollmayer and Noel or any combination thereof. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art (MPEP 2143.01.III, citing *KSR*, *supra*). For at least this reason, the present claims are not *prima facie* obvious over the cited art.

3.6. Conclusion

In sum, the Office has not established a presumption of *prima facie* obviousness of Claim 18 directed to a method for preparing a rotigotine-containing TTS because (1) the alleged combination does not teach all claimed features; (2) Chen cannot be a main §103(a) reference; (3) the cited publications are not combinable because teachings are incompatible; (4) there is no rationale to modify the cited art to include the missing subject matter; and (5) predictability of outcome required for *prima facie* obviousness is lacking.

Claims 20-25 depend directly or indirectly from Claim 18 and are, thus, non-obvious at least for the same reasons as Claim 18 is non-obvious. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Schollmayer and Noel is respectfully requested.

4. Rejection under 35 U.S.C. §103(a) over Chen in view of Schollmayer, Noel and Venkatraman

Claims 18 and 20–25 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Chen in view of Schollmayer, Noel and U.S. 2005/0048104 ("Venkatraman"). This rejection is respectfully traversed.

All reasons outlined above related to the 35 U.S.C. §103(a) rejection over Chen, in view of Schollmayer and Noel are applicable here. Particularly, Chen cannot be a main §103(a) reference. Furthermore, Venkatraman does not repair the deficiencies in the alleged combination of Chen, Schollmayer, and Noel since Venkatraman does not describe a method comprising dispersing and melting an active substance.

(1) Venkatraman describes a reservoir system which is incompatible with Chen and Noel. Therefore, Venkatraman is not combinable with the other three publications.

(2) Venkatraman relates to a TTS comprising fentanyl as an active ingredient. Fentranyl is structurally different from rotigotine and its physical, chemical and pharmacological properties are totally different from those of rotigotine. Therefore, Venkatraman's teachings are not applicable to the claimed invention.

(3) It is respectfully submitted that Venkatraman is not accurately characterized in the Office Action. The Office Action states that "Venkatraman teaches a hot melt process that protects active agent from degradation." (Office Action, pg. 12).

Venkatraman describes the following:

- "[o]ne problem associated with polyurethanes of the prior art is their high processing temperature, typically 170-250°C...[which preclude the] melt-mixing of most drugs into the polyurethane polymer to obtain a drug reservoir for a transdermal drug delivery system." (paragraph **[0015]**)
- "The drug reservoirs of the present invention comprise a polyurethane polymer which can be processed at temperature below those which cause degradation of temperature sensitive drugs and/or excipients" (Abstract)
- "[t]he polyurethanes of this invention can be processed at temperatures lower than about 150°C., preferably lower than about 100°C., and most preferably within about 40-90°C without the use of organic solvents" (paragraph [**0033**])

Venkatraman teaches that the active agent is not protected from degradation after the hot-melt process, but during the hot-melt process because of the normal operative temperatures permitted by the polyurethanes of Venkatraman. It is already known that rotigotine is very temperature-sensitive under normal hot-melt conditions. In this respect,

Venkatraman does not provide anything that was not already known at the onset. Rather, the surprising result was that rotigotine could undergo a hot-melt process at all. Venkatraman does not teach or suggest explicitly or implicitly that rotigotine could undergo a hot-melt process at any temperature.

Therefore, a presumption of *prima facie* obviousness has not been established with the alleged combination, and Claim 18 is non-obvious. Claims 20-25 depend directly or indirectly from Claim 18 and are, thus, nonobvious at least for the same reasons as Claim 18 is nonobvious. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Schollmayer, Noel and Venkatraman is respectfully requested.

5. Maintained Rejection under 35 U.S.C. §103(a) in previous Office Action

(1) Rejection under 35 U.S.C. §103 over Chen in view of Metman and Loper

As discussed above, Chen cannot be the primary §103(a) document relied upon because it does not teach any of the main features of the claimed method. Chen is not modifiable, and it is respectfully requested that all non-obviousness rejections based on Chen be withdrawn. In addition, there are some other facts to be considered as discussed below.

Chen in view of Metman and Loper fails to teach or suggest a method of preparing a TTS in which rotigotine as active substance is dispersed and melted using a hot-melt process. In particular, the alleged combination in the present rejection fails to teach or suggest infusing or dispersing any active substance including rotigotine without solvent wherein the active substance is melted. Thus, even if an ordinary skilled artisan attempted to combine the various disclosures of Chen, Metman and Loper (no admission is made herein that motivation would have existed for such combination), the combination would not provide all the features of the present claims.

Loper is incompatible with Chen. Chen describes a method for preparing a matrix-system using a solvent whereas Loper describes a reservoir system in which drug is dispersed in a non-adhesive matrix by a hot-melt process. For example, Loper describes that "[t]he components are the backing layer **11**, drug reservoir layer **12** consisting of drug **13** homogenously distributed as a molecular solution in a continuous matrix **14**, a membrane

layer **15** coextensive with the drug reservoir layer and along the surface opposite that occupied by the backing layer and optionally, but preferably, an adhesive layer **16** along the opposite surface of the membrane layer as a means for affixing the bandage to the skin." (col. 4, lines 27-36).

Furthermore, Loper fails to describe a method for preparing an active-substance-containing cement matrix. The drug reservoir layer does not contain adhesive. In fact, no adhesive component whatsoever is essential to the Loper TTS (col. 5, lines 52-56), whereas the claimed method for preparing a TTS requires a hot-meltable adhesive. Loper shows that it is the drug reservoir layer, not an active-substance-containing cement matrix, and that can be coated onto the backing material using hot-melt deposition (col. 8, lines 27-30). More importantly, the method of Loper for hot-melt deposition requires a solvent (col. 8, lines 20-22) in contrast to the presently claimed method for preparing a TTS without solvent.

There is no reasonable expectation of success with the alleged combination. As mentioned above, drug-loaded solid dispersion with high drug dissolution enhancement is not an easy task. Despite the difficulties, Applicant has provided a method for preparing a TTS that comprises a rotigotine-containing cement matrix with a high concentration of rotigotine and with high drug dissolution enhancement.

For the reasons above, a presumption of *prima facie* obviousness cannot be established with the alleged combination, and Claim 18 is non-obvious. Claims 20-25 depend directly or indirectly from Claim 18 and are, thus, nonobvious at least for the same reasons as Claim 18 is nonobvious. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Metman and Loper is respectfully requested.

(2) Rejection under 35 U.S.C. §103 over Chen in view of Metman, Loper and Noel

The combination of the Chen, Metman, Loper and Noel documents cannot establish a *prima facie* case of obviousness for Claim 18. The failure of a three-way combination of Chen, Metman and Loper to establish *prima facie* obviousness of the present claims is demonstrated above. Addition of Noel fails to cure the shortcomings of the three-way combination of Chen, Metman and Loper, and what is more, the Chen and Noel disclosures are incompatible and cannot be properly combined as no reason is provided as to how a skilled artisan would reconcile their disparate teachings.

Chen is incompatible not only with Loper, as discussed above, but also with Noel. Chen mentions a drug dispersed in an adhesive matrix by a non-hot-melt method whereas Noel shows a non-drug-containing adhesive matrix formed by a hot-melt process. Noel teaches a matrix-dispersion (col. 6, lines 8-15) and a reservoir system (col. 6, lines 16-64), but not a microreservoir system as Chen does.

The alleged combination fails to provide an apparent rationale by which an ordinary skilled artisan would modify the collective teachings to include the missing subject matter, and no reason based on the general knowledge in the art is identified by which an ordinary skilled artisan would be led to include the missing subject matter. Chen's use of ropinirole dissolved in water or other solvent and mixed with a polymer to form a reservoir layer is not modifiable with Metman, Loper or Noel. It is not clear how a person of ordinary skill would reconcile these disparate teachings without contravening the operation of one of these publications. Only the present specification and claims appreciate the surprising result of the claimed method that rotigotine remains stable in admixture (specification, paragraph **[0108]**).

Claim 18 and all claims dependent directly or indirectly therefrom are for reasons set forth above not obvious over the cited art. Withdrawal of the present 35 U.S.C. §103(a) rejection over Chen in view of Metman, Loper and Noel is respectfully requested.

6. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.